Published in final edited form as:

Ann Med. 2014 February ; 46(1): 8–17. doi:10.3109/07853890.2013.857831.

INVASIVE AND NON-INVASIVE TECHNIQUES FOR DETECTING PORTAL HYPERTENSION AND PREDICTING VARICEAL BLEEDING IN CIRRHOSIS: A REVIEW

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Abstract

Portal hypertension is a severe syndrome that may derive from pre-sinusoidal, sinusoidal and post-sinusoidal causes. As a consequence, several complications (i.e., ascites, oesophageal varices) may develop. In sinusoidal portal hypertension, hepatic venous pressure gradient (HVPG) is a reliable method for defining the grade of portal pressure, establishing the effectiveness of the treatment and predicting the occurrence of complications; however, some questions exist regarding its ability to discriminate bleeding from nonbleeding varices in cirrhotic patients. Other imaging techniques (transient elastography, endoscopy, endosonography and duplex Doppler sonography) for assessing causes and complications of portal hypertensive syndrome are available and may be valuable for the management of these patients.

In this review, we evaluate invasive and non-invasive techniques currently employed to obtain a clinical prediction of deadly complications, such as variceal bleeding in patients affected by sinusoidal portal hypertension, in order to create a diagnostic algorithm to manage them.

Again, HVPG appears to be the reference standard to evaluate portal hypertension and monitor the response to treatment, but its ability to predict several complications and support management decisions might be further improved through the diagnostic combination with other imaging techniques.

Keywords

liver cirrhosis; noninvasive assessment; portal hypertension; radiology; ultrasound

Introduction

Portal hypertension is due to enhanced portal vein pressure caused by prehepatic, intrahepatic or posthepatic resistance (1). In liver cirrhosis, portal hypertension begins when there is fibrotic disruption of the sinusoidal liver architecture and dynamic changes in the contractility of hepatic stellate cells (2). An impairment of peroxisome proliferator-activated receptors (3), and an imbalanced production of a number of vasoactive mediators, may cause the development of intrahepatic vascular shunts, contributing to the severity of portal hypertension and its complications, and favouring the development of a hyperdynamic circulation (4–6).

Despite an absolute increase in blood volume, there is a state of functional hypovolemia and then to compensate for it, the sympathetic nervous system is strongly activated, leading to sodium and water retention that worsens portal hypertension and favours ascites production (7–9). At the same time, kidney imbalances and hepatorenal syndrome may develop (9), as well as, portosystemic shunts; the development of varices is strongly favoured when increased reversal inflow involves the gastric veins. Because the prevalence of varices is high in cirrhotics (10,11), knowing the grade of portal hypertension is important.

Today, the measurement of hepatic venous pressure gradient (HVPG) is considered a safe procedure to indirectly individuate the portal pressure and monitor the portal hypertension. An HVPG value above 5 mmHg is suggestive of portal hypertension (12). HVPG accurately reflects the portal pressure, but some variables may influence its reliability in predicting variceal bleeding. HVPG, in some circumstances, does not reach clinical utility, at which point employing other methods might add helpful information.

We aim to review available data regarding the ability of HVPG to assess portal hypertension and the risk of variceal bleeding by comparing this invasive method to other non-invasive and invasive methods that are also available for this purpose.

Hepatic Venous Pressure Gradient

Wedge hepatic venous pressure (WHVP), a measurement of the sinusoidal pressure obtained by inflating a balloon tipped catheter in a hepatic vein and stopping blood flow, was correlated to portal pressure (13). Now, it has been elucidated that WHVP underestimates portal pressure when the portal hypertension is due to pre-sinusoidal causes (14,15); indeed, in pre-sinusoidal portal hypertension, the free hepatic venous pressure (measured with the deflated catheter tip lying freely in the hepatic vein) and WHVP are both normal. On the contrary, they are both increased in post-sinusoidal portal hypertension, whereas in sinusoidal ones, only WHVP is increased (14,15).

Ability to predict portal pressure

Several years ago, it was questioned whether measurement of WHVP might be incorporated into clinical practice (16). Some authors now debate that in sinusoidal portal hypertension, the intravariceal pressure is similar to the WHVP, and consequently, the wall tension will be directly proportional to it and not to HVPG (17); therefore, in their opinion, the

measurement of WHVP is the correct method to evaluate the risk of variceal rupture and should be reported in the diagnosis together with HVPg when a haemodynamic portal hypertension study is performed (17).

On the other hand, HVPg (i.e., the difference between the wedged hepatic venous pressure and free hepatic venous pressure) (13–17), gives an idea of the amount of blood flow that may travel through varices. Indeed, HVPg is the gradient between portal vein and intra-abdominal vena cava pressure. Therefore, HVPg gives the exact degree of portal hypertension in the portal venous system in sinusoidal portal hypertension and provides important information in other cases (pre- and post-sinusoidal). HVPg is normal in pre-sinusoidal portal hypertension, whereas it is mildly to moderately and severely increased when portal hypertension is due to post-sinusoidal and sinusoidal causes, respectively (14). When the HVPg is above 10–12 mmHg (9), it has a valuable prognostic role in predicting variceal haemorrhage or ascites formation and death in cirrhotic patients with bleeding varices (18,19).

Outcomes

Follow up with HVPg is important to monitor the efficacy of medical treatment. Some meta-analyses have demonstrated that a reduction of HVPg to <12 mmHg or more than 20% of baseline significantly reduces the risk of bleeding (19–22), whereas HVPg values equal to or below 8 mmHg are expected to control refractory ascites (23). More than 95% of transplanted liver patients with an HVPg below 6 mmHg do not face a risk of decompensation in the next three years (24).

The worsening of HVPg in good responders to medical treatment was related to worsening in hepatic function (25).

To assess the response to treatment, two HVPg measurements at an interval of at least a few weeks are necessary; however, diffusion and feasibility of the HVPg in routine clinical practice is limited due to several factors: invasiveness of the procedure, bad compliance of the patients, low availability in general hospitals and excessive costs (26).

Some controversies exist about the role of HVPg in discriminating bleeding and non-bleeding varices in cirrhotic patients (27). Comparing HVPg values in patients with only large varices with or without bleeding demonstrated statistically significant differences; however, the reliance of HVPg as a predictor of variceal bleeding remains debatable because both patients with non-bleeding and bleeding large varices had similar high values of portal pressures (27). Therefore, the most important predictors of increased values of HVPg were Child-Pugh score, bleeding status, and size of varices (27).

Elastographic techniques

The principles, interpretation of the results, limitations and reproducibility of elastographic techniques are reviewed in the cited references (28,29).

1. Transient elastography

Transient elastography (TE) is a novel, non-invasive, safe and easy to perform technique that gives information on the level of fibrosis by measuring liver stiffness through the transmission of mechanical waves into the liver tissue and after analysis of the wave propagation and liver tissue deformation (28–33). Obesity, presence of ascites and increase of the ALT value, are all limiting factors that may impede a precise measurement of liver stiffness. In some cases, discordance was found between the results of TE and those of liver biopsy in diagnosing cirrhosis; large disagreement also exists in establishing a cut-off value of liver stiffness that is able to provide a proven diagnosis of cirrhosis (28–33). However, in a large retrospective study, liver stiffness values significantly correlated with Child-Pugh score and clinical and biochemical parameters of liver disease severity (31).

Ability to predict portal pressure and varices—Liver stiffness reveals the grade of portal hypertension and thus predicts the presence of varices, but unfortunately, the cut-off value overlaps with that for detecting cirrhosis (34). A strong correlation comparing liver stiffness and HVPG in diagnosing portal hypertension was found when HVPG was below 10 mmHg and not when HVPG was above 12 mmHg (35).

However, a recent meta-analysis from 18 studies, showed the utility of TE for detecting significant portal hypertension (> 10 mmHg) (36).

2. Acoustic radiation force impulse (ARFI) elastography

Acoustic radiation force impulse quantification (ARFI) may complete any B-mode liver ultrasound scan and give information on the severity of liver fibrosis, using short-duration acoustic pulses (push-pulses) emitted at approximately 2.6 MHz (29).

The lack of a direct comparison with HVPG does not permit any conclusion on the role of ARFI in predicting the presence of portal hypertension.

The mean shear wave velocity measured in the spleen demonstrated a good correlation with the portal vein pressure measured with HVPG, in 10 patients with cirrhosis who underwent TIPS placement for the treatment of portal hypertension (37). However, spleen elastography is inferior to liver elastography for the detection of portal hypertension (38).

An interesting algorithm, which includes the liver and/or spleen stiffness, was assessed using ARFI for predicting significant varices (at least grade 2) (39). The ability to predict the presence of large varices was good but not sufficiently high to replace gastroscopy for the screening of varices.

More recently, a cutoff spleen stiffness of 3.18m/s has been indicated to predict the presence of varices; according to the authors ARFI imaging may be an initial noninvasive screening test for predicting varices (40).

3. Two dimensional shear wave elastography (2D-SWE)

Two dimensional shear wave elastography (2D-SWE) detects shear waves in the liver tissue generated by the acoustic radiation force obtained with focalized ultrasound pulses (29).

A potential advantage of this technique is to provide information on shear wave speed in a two-dimensional area of few centimeters with better accuracy in comparison to TE in demonstrating presence of liver fibrosis (29).

No studies exist on the utility of 2D-SWE for detecting the presence of portal hypertension and varices.

4. Strain elastography (SE)

Strain elastography (SE) measures the tissue deformation induced by a stress providing qualitative information (color-coded mapping) on stiffness.

The utility of SE for detecting portal hypertension was reported in a study showing a correlation between spleen elasticity and portal pressure measured as HVPG (41).

Outcomes—Despite a good sensitivity in predicting varices, liver stiffness measurements of elastographic techniques are lacking in specificity and positive predictive value and thus are not enough reliable in clinical practice (34).

The Baveno IV consensus conferences recommended the development of non-invasive tools for diagnosing clinically relevant portal hypertension and monitoring the response to treatment (42,43). In light of this recommendation, the measurement of liver stiffness might be one of these methods; unfortunately, its reliability in giving information helpful to manage patients with portal hypertension is still low. The recent validation of a new non-invasive scoring system for detecting high-risk varices based on the measurement of liver stiffness and spleen diameter to platelet ratio might lead to the direction indicated by Baveno IV consensus conference (44).

Duplex Doppler Sonography

Duplex Doppler sonography evaluates the vascular system of cirrhotics, the presence of portal hypertension and its complications, but experience and practice are required and some issues are raised about this procedure (45).

Ability to predict portal pressure

The simultaneous presence of a vascular enlargement in the spleno-mesenteric and portal axis indicated the presence of varices with high sensitivity and specificity (46).

Unfortunately, most cirrhotics with varices have not a significantly enlarged spleno-mesenteric portal axis.

An increased portal vein diameter (more than 13 mm) was proposed as an independent predictor of varices by some authors but not by others (47–50).

A decreased portal flow volume is associated with portal hypertension and poor liver function in cirrhotics (it might predict variceal bleeding) (51,52), although there is disagreement (53,54). Splenic venous flow exceeding portal venous flow was implicated in the formation of varices and their bleeding (55).

The presence of monophasic waveforms in hepatic veins, correlates with higher Child–Pugh scores and decreased survival rates (54,56). Portosystemic shunts are also considered important complications of portal hypertension (57).

The reverse flow in the left gastric vein, a finding frequently associated with large varices, or the presence of splenorenal or combined shunts, which have been associated with severe and intermediate disease phases of cirrhosis (50,58), might be an indication to shorten intervals between endoscopic screening (59).

A large diversion of the portal flow into the left gastric vein favours varices and the occurrence of bleeding (60,61). Indeed, a close relation between the diameter of the left gastric vein and the size of varices as well as between the hepatofugal flow velocity in the left gastric vein and the risk of variceal bleeding has been demonstrated (56). Conversely, the absence of portosystemic shunts or the presence of only the umbilical vein is probably associated with a low risk of the occurrence of varices (50,60,62,63).

In compensated cirrhotics, both a portal hypertensive index of >2.08 and spleen size of >15.05 cm independently predicted the presence of varices (64).

Other haemodynamic indices by duplex Doppler sonography were increased in cirrhosis, but no correlation was found with HVPg values of 10–12 mmHg (65–67).

On the other hand, the highest accuracy in predicting portal hypertension, the presence of varices and the risk of bleeding might be provided by the measurement of combined indices such as splenoportal and portal hypertension indices (Table 1) (68–71).

Assuming that portal pressure derives from mean portal flow volume multiplied by the resistance to the flow, a non-invasive estimate of portal pressure was proposed by means of the Doppler sonographic measurement of splenic impedance indices and portal flow volume (Table 1) (72).

The hepatic vein arrival time (HVAT) is the time (in seconds) taken for the microbubble contrast agent to arrive at the hepatic vein after injection. Interestingly, it was reported that HVAT value, achieved by microbubble contrast enhanced sonography, well correlate with the degree of portal pressure and varices (73).

Outcomes

- Monophasic waveforms correlates with an HVPg of 15 mmHg and predicts the presence of severe portal hypertension with 74% sensitivity and 95% specificity (56).
- Enlarged diameter and increased flow velocity and volume in the short gastric vein predict gastric variceal bleeding (61).
- The contemporary presence of a decreased portal flow and increased portal and splenic congestion indices is related to a poor liver function predicting variceal bleeding (52).

- HVAT predicts the degree of portal pressure and the presence of varices (73)

Endoscopy and Endosonography

The onset of varices and the consequent bleeding risk are important complications of portal hypertension. Variceal wall tension, is the crucial mechanism underlying their rupture (74).

The severity of liver dysfunction, large size of varices and endoscopic red colour signs are important risk factors for the beginning of variceal bleeding, but unfortunately, they are only present in 1/3 of bleeding varices (75).

Varices affect approximately 60–85% of decompensated and 30–40% of compensated cirrhotics (10,76), and the prevalence of large varices in the latter is approximately 35% (77).

Small varices with endoscopic red colour signs also need treatment because of the risk of bleeding (42,78).

Strategies aimed at identifying non-invasive tools to recognise bleeding risk were attempted; unfortunately, in well-compensated cirrhotics, the non-invasive prediction of varices and bleeding risk lacks accuracy, and as a result, endoscopic surveillance cannot be avoided in the majority of cirrhotics (48).

Ability to predict variceal pressure

A method for the measurement of intravariceal pressure to predict variceal bleeding was developed (79). Subsequently, thanks to the availability of endosonography (EUS), the study of varices improved. Variceal wall thickness and radius were measured through high-resolution EUS (80,81). Variceal wall tension was obtained by combining data acquired by intravariceal needle puncture with those given by high-resolution EUS (82). Although variceal wall tension was very useful for predicting initial or recurrent variceal bleeding, the risk of bleeding with variceal needle puncture was too high. To avoid this risk, multiple minimally invasive techniques for the measurement of intravariceal pressure were developed (83,84); unfortunately, each one required specialised equipment as well as standard endoscopy and manometry, making their large scale utilisation in endoscopic units difficult.

A simpler means to predict future variceal bleeding was the measurement of the total cross-sectional surface area of varices using EUS (85).

Since variceal rupture occurs when outwardly expanding forces in the variceal lumen exceed the maximal wall tension of the variceal wall, a new minimally invasive method to measure intravariceal pressure was proposed, requiring only an endoscope and a pressure transducer (84). Because intravariceal pressure equals the extravariceal pressure at variceal flattening, quantifying the flattening pressure by measuring esophageal lumen pressure at the start of variceal flattening, may give the intravariceal pressure (85). Variceal wall tension was also calculated by measuring variceal radius and wall thickness with high-resolution EUS; a strong correlation was found between wall tension and variceal radius but not with wall

thickness, thus confirming the inability to accurately estimate variceal wall tension by combined EUS and intravariceal pressure measurements (86).

Outcomes

High-resolution EUS clearly examines the variceal wall and may demonstrate the haematocystic spots that are saccular aneurysms protruding on the variceal surface; they were assumed to be focal weaknesses of the variceal wall that favour the variceal rupture (87).

Magnetic resonance studies demonstrated that azygos blood flow correlated with the presence of and the risk of bleeding from oesophageal varices (88). EUS showed the vascular anatomy of varices surrounding the oesophagus and proximal stomach [ascertaining that large paraoesophageal and paragastric varices (5 mm or greater) are risk factors for variceal haemorrhage] and revealed presence of collaterals and diameter of the azygos vein (89,90).

A colour Doppler EUS investigation demonstrated that in cases of bleeding varices, the blood flow velocities in gastric varices were significantly higher than those in nonbleeding varices (91).

Magnetic resonance elastography (MRE)

Magnetic resonance elastography (MRE) is an MRI-based technique for quantitatively assessing the tissue elasticity, using propagating mechanical shear waves (92).

Principles, interpretation of the results, limitations and reproducibility of MRE is extensively reviewed in the cited reference (92).

MRE studies in animal models of fibrosis and in patients with cirrhosis (92–95) demonstrated that

- the detection of stiffness is not influenced by the presence of steatosis
- this method has an excellent diagnostic accuracy for assessing liver fibrosis (sensitivity and specificity of 98% and 99% for detecting all grades of liver fibrosis, respectively).

Ability to predict portal pressure

By using MRE, a higher spleen stiffness and strong correlation between hepatic and splenic stiffness were demonstrated in patients with cirrhosis (95).

In a canine model of portal hypertension the MRE-assessed stiffness of the spleen was in correlation with the magnitude of the HVP (96).

Furthermore, a significant increase of MRE-assessed liver stiffness was showed following a test meal in patients with advanced liver fibrosis (97).

These results suggest a role for MRE in detecting portal hypertension; however, further studies are needed to confirm these data.

Laboratory tests

The combination of laboratory tests represents another noninvasive, low cost and independent of expertise method that shows correlation with HVPG and may detect the presence of varices (98).

Ability to predict portal pressure and varices

In compensated cirrhosis, a model combining albumin, ALT and INR showed a good ability to clinically predict significant portal hypertension (48).

Fibrotest (Biopredictive, Paris, France), a panel of five biochemical markers of hepatic fibrosis, combined with age and gender, is a good predictor of liver fibrosis. Fibrotest has demonstrated to have a moderate diagnostic value in estimating severe portal hypertension in cirrhotics (99).

A HOMA score > 4 has a good ability to predict the presence of varices (100). A positive correlation is present between HOMA-IR and HVPG (100).

A low platelet count is the most useful test to predict the presence of varices (101).

Combination tests

By combining three simple measurements (liver stiffness, spleen size and platelet count) so that a single score is obtained, a good accuracy for diagnosing and ruling out varices and portal hypertension in patients with cirrhosis was achieved (44,102).

Conclusion

HVPG and endoscopy are again considered the best systems to determine the exact degree of sinusoidal portal hypertension and to detect the presence of varices (Table 2–4).

The Baveno V consensus conference recommended no satisfactory non-invasive tools on portal hypertension because of insufficient data (43); endoscopic screening and HVPG are still considered the best practice to detect the presence of varices and to predict variceal development and should be routinely used for prognostic and therapeutic indications (34,41,43).

Cirrhotics should receive screening endoscopy within 6 months of their initial visit to a liver centre (20,103). Cirrhotics also should be treated with a noncardio-selective beta-blocker or have variceal ligations when needed; follow-up upper intestinal endoscopy should be performed at appropriate intervals post-oesophageal variceal ligation and for routine surveillance (103).

Beta-blockers should be administered to the maximum tolerated dose (103).

Patients with cirrhosis and gastrointestinal bleeding should have upper endoscopy as soon as possible after admission (within 12 h) (43).

Management in accordance to practice guidelines is associated with a lower bleeding rate than that expected in untreated patients (103,104).

A possible diagnostic algorithm for new cirrhosis diagnosis is showed (Figure 1).

From this algorithm it emerges that noninvasive methods have a restricted field of applicability in clinical practice. Therefore, progress in non-invasive methods are desirable to prevent from performing frequently upper endoscopy and HVPG measurements.

To date, guidelines (Baveno V) and advantages and disadvantages of different available tools (see Table 4) recommend the use of endoscopy and HVPG to detect varices and portal hypertension.

Additional research/data are needed to ameliorate noninvasive diagnosis of varices and portal hypertension. It is necessary to develop noninvasive methods able to accurately predict portal hypertension <12 mmHg and to detect presence of varices; at the same time, these methods should also have good accuracy in predicting portal hypertension >12mmHg and presence of varices that are at a high risk for bleeding. Since portal hypertension is the major cause of development of varices and their bleeding, new pharmacological therapeutic strategies aimed to reduce portal pressure would be also needed.

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Key Messages

- Endoscopic screening is the best practice to detect the presence of varices and should be routinely used for prognostic and therapeutic indications.
- HVPG is an important tool to predict variceal development, haemorrhage or ascites formation and death in cirrhotics and should be routinely used for prognostic and therapeutic indications.
- Until now, no satisfactory non-invasive tools for diagnosing clinically relevant portal hypertension and presence of varices; additional research to ameliorate noninvasive diagnosis of varices and portal hypertension are desirable.

Figure 1.

Table 1

Sonographic Doppler indices for predicting portal hypertension, varices and bleeding

Measurement	Formula	References
Portal congestion index	CSApv/portal flow velocity	Moriyasu F, 1986
Splenic congestion index	CSAsv/splenic flow velocity	Xiao-Yu Yin, 2001
Portal vascular resistance	$(0.066 * \text{splenic PI}) - 0.044$ (mmHg ml ⁻¹ sec)	Bolognesi M, 2001
¹ Estimated portal pressure	PVR * PFV (mmHg)	Bolognesi M, 2001
Portal hypertension index	$[(\text{HA-RI} * 0.69) * (\text{SA-RI} * 0.87)] / \text{PFV (m/s}^{-1})$	Piscaglia F, 2001
² Splenoportal index	SI / PFV (cm/s)	Liu CH, 2008
Liver vascular index	Portal flow velocity/HA-PI	Iwao T, 1997
Modified liver vascular index	Portal flow velocity/HA-RI	Piscaglia F, 2001

CSApv: cross-sectional area of portal vein; **CSAsv:** cross-sectional area of splenic vein; **HA-PI:** hepatic artery-pulsatility index; **HA-RI:** hepatic artery-resistance index; **PI:** pulsatility index [(systolic velocity - end diastolic velocity)/mean velocity]; **PVR:** portal vascular resistance; **PFV:** portal flow volume; **RI:** resistance index [(systolic velocity - end diastolic velocity)/systolic velocity]; **SA-RI:** splenic artery-resistance index; **SI:** splenic index (cross sectional area of the spleen)

¹This method facilitated the differentiation of mild (HVPG <16 mmHg) from severe (HVPG >16 mmHg) portal hypertension,⁷⁰ but it was not able to give a precise value of portal pressure in an individual patient; furthermore, because a cut-off value of >12 mmHg is currently used to predict the risk of bleeding, it is clear that a cut-off value of 16 mmHg is too high to be useful.

²When the cut-off value of the splenoportal index was set to 3, sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy in predicting oesophageal varices were 92%, 93%, 91%, 94% and 93%, respectively.

Table 2

Performance of different methods in predicting portal hypertension ($> 10\text{mmHg}$), in comparison to HVPG.

<u>METHODS</u>	<u>No. Pts</u>	<u>Best cut off values</u>	<u>Se%</u>	<u>Sp%</u>	<u>PPV%</u>	<u>NPV%</u>	<u>Accuracy</u>	<u>AUTHORS</u>
Transient elastography	420 from 5 studies	From 13.6 to 34.9 kPa	90	79	88	88		Shi KQ, (2013)
ARFI	30	1.67m/s	80	92	75	94		Rifai K, (2011)
2D-SWE	-	-	-	-	-	-	-	-
Strain elastography	270	8.24	96	85	83	97	90	Hirooka M, (2011)
Duplex Doppler sonography	21	$< \text{or} > 16 \text{ mmHg}$	82	70	75	78		Bolognesi M, (2001)
CEUS	71	14 seconds	92.7	86.7	90.5	89.7	90	Kim MY, (2012)
EGD	52		57.7	100	100	88.3		Lee YT, (2002)
EUS	52		92.3	94.6	84.2	97.5		Lee YT, (2002)
MRE	-	-	-	-	-	-	-	-
Fibrotest	92	>0.93	88	50	94	30	-	Thabut D, (2007)
HOMA-IR	-	-	-	-	-	-	-	-
Platelet count	-	-	-	-	-	-	-	-
Combined test	173	1.72	83.3	84.6	91.5	71.7	83.7	Berzigotti A, (2013)

ARFI= Acoustic radiation force impulse elastography;

CEUS= Contrast enhanced sonography;

Combined test= combination of three measurements (liver stiffness $\times$ platelet count to spleen diameter ratio);

EGD= esophagogastroduodenoscopy;

EUS= endosonography;

Fibrotest= A panel of five biochemical markers of hepatic fibrosis ($\alpha 2$ -macroglobulin, haptoglobin, gamma glutamyl transferase, total bilirubin, and apolipoprotein A1) combined with **age, and gender**;

HOMA-IR = fasting insulin ($\mu\text{U/mL}$) $\times$ fasting glucose (mmol/L)/22.5;

HVPG= hepatic venous pressure gradient;

MRE= Magnetic resonance elastography;

PPV= positive predictive value;

Pts= patients;

NPV= negative predictive value;

Se= sensitivity;

Sp= specificity;

2D-SWE= two dimensional shear wave elastography.

Table 3
Performance of different methods in predicting esophageal varices compared to Endoscopy.

METHODS	PTS	Values	Accuracy	Se%	Sp%	PPV%	NPV%	AUTHORS
HVPG	69	a HVPG decrease to 12mmHg or 20% from baseline	-	52	92	-	-	Feu F, 1995
Transient elastography	2049 from 9 studies	from 17.8 to 48.0 kPa.	-	86	59	79	66	Shi KQ, (2013)
ARFI	132	> 2.25 m/s 3.18 m/s	56.5 75	93.4 98.5	28.9 60.1	49.5 61	85.7 98.4	Bota S, (2012) Takuma Y, (2013)
2D-SWE								
Strain elastography	270	8.24	90	96	85	83	97	Hirooka M, (2011)
Duplex Doppler sonography	28	Monophasic waveform of hepatic vein	-	74	95	-	-	Baik SK, (2006)
CEUS	-	-	-	-	-	-	-	-
EUS	52	-	-	96.4	95.8	96.4	95.8	Lee YT, (2002)
MRE	17	Mean value of 12.6 ± 2.0 kPa.-	-	41	-	-	-	Talwalkar JA, (2009)
Fibrotest	175		87.3	82.4	93	67	-	Eslam M, et al (2013)
HOMA-IR	175	> 4	-	89.7	71	74.3	88	Eslam M, et al (2013)
Platelet count	175	<100 10 ³ /mm ³	-	82.1	75.4	83.6	75.8	Eslam M, et al (2013)
Combined test	70	3.21	84.6	81.1	86.3	73.2	90.8	Berzigotti A, (2013)

ARFI= Acoustic radiation force impulse elastography;

CEUS= Contrast enhanced sonography;

Combined test= combination of three measurements (liver stiffness × platelet count to spleen diameter ratio);

EUS= endosonography;

Fibrotest= A panel of five biochemical markers of hepatic fibrosis (α2-macroglobulin, haptoglobin, gamma glutamyl transferase, total bilirubin, and apolipoprotein A1) combined with age, and gender;

HOMA-IR = fasting insulin (μU/mL) × fasting glucose (mmol/L)/22.5;

HVPG= hepatic venous pressure gradient;

MRE= Magnetic resonance elastography;

PPV= positive predictive value;

NPV= negative predictive value;

2D-SWE= two dimensional shear wave elastography.

Sp= specificity;

Se= sensitivity;

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Table 4

Summarization of advantages and disadvantages of different methods used in clinical practice and research for portal hypertension and varices determination.

Methods	Advantages	Disadvantages
HVPG	<ul style="list-style-type: none"> • Safe procedure • Good diagnostic accuracy • Gold standard for portal pressure measurement • Possibility of associating other procedures: transjugular liver biopsy, hepatic blood flow, measurement of right atrial pressure, pulmonary artery pressure, wedged pulmonary pressure and cardiac output • Independent predictor of outcomes in cirrhotics • It provides prognostic information: on cirrhotics awaiting liver transplantation, independent of Meld score, on short term outcomes of patients with alcoholic hepatitis • Gold standard to assess new therapies and noninvasive methods designed to treat or evaluate portal hypertension 	<ul style="list-style-type: none"> • Invasive • Not available at every Hospital • Expensive • Learning curve • Complications: leakage, hematoma, vagal reactions, rupture of venous introducers, arteriovenous fistulae, air embolism, pneumothorax, hemothorax, deep vein thrombosis, femoral arterial puncture • It does not allow direct visualization of varices
Transient elastography	<ul style="list-style-type: none"> • Rapid, noninvasive • Available • Highly reproducible • Good diagnostic accuracy 	<ul style="list-style-type: none"> • Difficult to perform in obese patients and cirrhotics with ascites • Lack of visualization of the studied area • It is possible to analyze only a small portion of the liver • This system is not incorporated in conventional ultrasound machine • The machine is expensive • A learning curve is necessary • It does not allow grading of portal pressure and direct visualization of varices
ARFI	<ul style="list-style-type: none"> • Rapid, noninvasive • Available • Highly reproducible • Good diagnostic accuracy • Ability to control measurement and depth • It is incorporated in conventional ultrasound machine 	<ul style="list-style-type: none"> • It requires an acoustic window • Measurements are not retrospective and are not in real time • The measurement is only one at a time • It is possible to analyze only a small portion of the liver • No standard deviation is given among the results • No validation has been so far obtained • It does not allow grading of portal pressure and direct visualization of varices
2D-SWE	<ul style="list-style-type: none"> • Rapid, noninvasive • Easy to perform 	<ul style="list-style-type: none"> • Further validation is needed • It does not allow grading of portal pressure and direct visualization of varices

Methods	Advantages	Disadvantages
	<ul style="list-style-type: none"> • Available • Highly reproducible • Quantitative assessment (kPa or m/s) • Ability to control measurement and depth • Ability to perform measurements retrospectively • Ability to decide the size of the box 	<ul style="list-style-type: none"> • It is possible to analyze only a small portion of the liver
Strain elastography	<ul style="list-style-type: none"> • Easy to perform, noninvasive • Available • Suitable for use in clinical setting • Incorporated in conventional ultrasound machine 	<ul style="list-style-type: none"> • It requires an acoustic window • Difficult to perform in obese patients and cirrhotics with ascites • In most of conventional ultrasound machine, the elastogram may be displayed only as a color-overlay on the B-mode picture • Lack of quantification • It is possible to analyze only a small portion of the liver • The measurements are operator dependent • It does not allow grading of portal pressure and direct visualization of varices
Duplex Doppler sonography	<ul style="list-style-type: none"> • Quite rapid, noninvasive • Available • Quantitative assessment • Noninvasive investigation of portal hypertension 	<ul style="list-style-type: none"> • It requires an acoustic window • A learning curve is necessary • Experienced operators • Not sufficiently sensitive or specific to replace HVPg • It does not allow grading of portal pressure and direct visualization of varices
Contrast enhanced sonography	<ul style="list-style-type: none"> • Reproducible • Safety • Noninvasive prediction of portal hypertension • Good correlation with HVPg measurement in compensated cirrhotics • Supplementary tool when HVPg cannot be done 	<ul style="list-style-type: none"> • The kind of software may influence the results • It requires an acoustic window • Difficult to perform in obese patients • No good correlation with HVPg in decompensated cirrhotics • It requires respiratory cooperation • A learning curve is necessary
EGD	<ul style="list-style-type: none"> • Gold standard for detection and surveillance of varices in cirrhotics • Standard endoscopy with air insufflation and manometry can be used to measure intravariceal pressure 	<ul style="list-style-type: none"> • Invasive • Low tolerance without sedation • Complications: perforation, bleeding, heart or lung failure • It does not allow grading of portal pressure
EUS	<ul style="list-style-type: none"> • A good technique for evaluating periesophageal circulation 	<ul style="list-style-type: none"> • Invasive • Same intolerance and complications of EGD

Methods	Advantages	Disadvantages
	<ul style="list-style-type: none"> • It may help in localizing bleeding varices and guiding endoscopic therapy • Prognostic information on variceal recurrence and rebleeding after treatment • Quite promising animal studies on portal pressure measurement 	<ul style="list-style-type: none"> • No human studies on grading of portal pressure • No validated studies on measurement of variceal pressure
MRE	<ul style="list-style-type: none"> • Noninvasive • Data acquisition is operator independent • Staging of liver fibrosis • Suitable for evaluation of obese patients • It does not require an acoustic window • The whole liver is visualized 	<ul style="list-style-type: none"> • Expensive • It measures a surrogate of liver fibrosis (stiffness) • Wave interference and attenuation may compromise correct measurements • It does not allow grading of portal pressure and direct visualization of varices • Lack of standardization
Fibrotest	<ul style="list-style-type: none"> • Noninvasive validated marker in the detection of liver fibrosis • Significant relationship with the presence of varices • Good relationship with HVP 	<ul style="list-style-type: none"> • Alone, it is not a recommended predictive marker of severe portal hypertension in cirrhotic patients • In cirrhotics with alcoholic hepatitis, higher values of bilirubin and lower values of apolipoprotein A1 may influence the test • In cirrhotics with ascites, lower values of α_2 macroglobulin may influence the test • It does not allow grading of portal pressure and direct visualization of varices
HOMA-IR	<ul style="list-style-type: none"> • Noninvasive, inexpensive • Independent predictor of the presence of varices • It predicts variceal bleeding risk • It may help clinical decision-making regarding the need for and the timing of endoscopy 	<ul style="list-style-type: none"> • It does not allow grading of portal pressure and direct visualization of varices
Platelet count	<ul style="list-style-type: none"> • Noninvasive, inexpensive • Independent predictor of the presence of varices • It may help clinical decision-making regarding the need for and the timing of endoscopy 	<ul style="list-style-type: none"> • It does not allow grading of portal pressure and direct visualization of varices
Combined test	<ul style="list-style-type: none"> • Noninvasive • Good diagnostic performance for predicting varices, superior to that of liver stiffness alone • Low predicting probability of varices may delay performing endoscopy 	<ul style="list-style-type: none"> • It does not allow grading of portal pressure and direct visualization of varices • All disadvantages of liver stiffness measurement

ARFI= Acoustic radiation force impulse elastography;

CEUS= Contrast enhanced sonography;

Combined test= Combination of three measurements (liver stiffness $\times$ platelet count to spleen diameter ratio);

EUS= Endosonography;

Fibrotest= A panel of five biochemical markers of hepatic fibrosis (alpha2-macroglobulin, haptoglobin, gamma glutamyl transferase, total bilirubin, and apolipoprotein A1) combined with **age, and gender**;

HOMA-IR = Fasting insulin ($\mu\text{U/mL}$) $\times$ fasting glucose (mmol/L)/22.5;

HVPG= Hepatic venous pressure gradient;

MELD= Model for end stage liver disease;

MRE= Magnetic resonance elastography;

PPV= Positive predictive value;

NPV= Negative predictive value;

Se= Sensitivity;

Sp= Specificity;

2D-SWE= Two dimensional shear wave elastography.